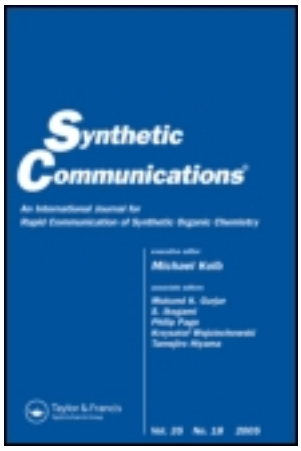

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Preparation of a Series of Aryl Isonipecotic Acids Using Microwave Irradiation

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ABSTRACT

Rapid parallel synthesis of arylisonipecotic acids was achieved using microwave irradiation of a palladium catalyzed amination reaction.

Aryl isonipecotic acids (**3**) are useful intermediates in the preparation of a wide range of potential drug agents such as anticoagulants,[1] platelet aggregation inhibitors,[2] fibrinogen receptor antagonists,[3] antimicrobial agents,[4] neuropeptide Y antagonists,[5] and serotoninergic/dopaminergic receptor antagonists.[6] These isonipecotic intermediates are generally prepared by aromatic nucleophilic substitution that requires the presence of an electron withdrawing (NO_2, COOR) group on the aromatic ring. Alternatively, displacement of pyridinium salts[6] allows for the presence

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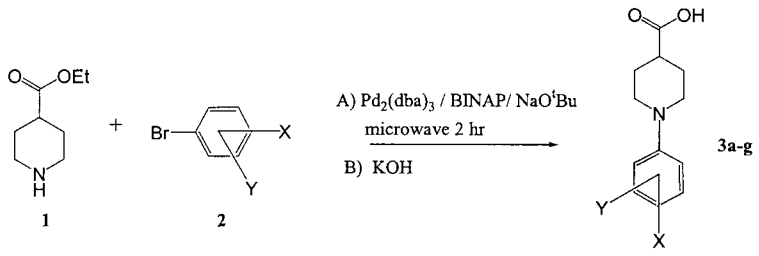
of electron releasing groups, but overall yield is low due to the difficulty in reducing the pyridinium salts to piperidines. Generation of aryl amines by coupling of simple amines and variously substituted aryl bromides using palladium catalysis has been established by Guram et al.[7] and Louie and Hartwig.[8]

Recently Hallberg and Larhed[9] have utilized a method for microwave assistance in several palladium-catalyzed reactions (Heck, Stille and Suzuki coupling) for combinatorial synthesis and the production of chemical libraries. So far, however, there have been no reports on the Buchwald-Hartwig[10] reactions facilitated by microwave irradiation. Described below is a palladium catalyzed coupling of an amino ester (**1**) with aryl bromides (**2a**–**g**) effected in a minimum of solvent using microwave irradiation.

The reactions are shown in Sch. 1 and results are summarized in Table 1. Multiple parallel reactions were conveniently assembled using the 36-position high throughput accessory (CEM Corp.). The number of vessels used in the microwave carousel did not adversely affect product yields or reaction time as long as temperature was controlled via a fiber optic probe. Also scale up of a single reaction is possible by utilizing several



Scheme 1.

Table 1. Preparation of aryl isonipecotic acids.

Compound **3**	X	Y	Yield (%)
a	4-CF_3	H	50
b	3-CN	H	55
c	3-F	5-F	35
d	3-CF_3	5-CF_3	53
e	2-F	5-CH_3	45
f	2-OCH_3	H	52
g	2-CH_3	H	45

vessels with the same reagents. The resultant oily esters were hydrolyzed to the corresponding acids (**3a**–**g**) as solids for characterization.

EXPERIMENTAL

Microwave irradiations were carried out using a CEM MDS 2000 microwave instrument equipped with a fiber optic temperature probe and a high throughput accessory (carousel of 36×50 mL centrifuge tubes). ^{1}H NMR spectra (400 MHz) were recorded in d_6-DMSO using a Varian Unity plus spectrometer. Mass spectra were recorded on a MAT900 icis 8.2.1. Aryl bromides (**2a**–**g**) and isonipecotic acid ethyl ester were commercially available from Aldrich.

General Procedure

A mixture of BINAP (100 mg, 3 mol%), NaO^{t}Bu (600 mg, 6.06 mmol), $Pd_2(dba)_3$ (50 mg, 1 mol%), ethyl isonipecotate (880 mg, 5.60 mmol) and aryl bromide (5.00 mmol) are diluted with toluene to a total volume of 10 mL in a 50 mL centrifuge tube. Each tube is agitated and placed into the high throughput carousel and irradiated at 750 W in three stages of 40 min each (maximum temperature allowed 110°C). The crude mixture was absorbed onto silica gel and subjected to flash column chromatography (hexane/ethyl acetate). The oily ester product (2 mmol) was then hydrolyzed in THF (28.8 mL) and methanol (7.2 mL) with 1 N KOH (2.4 mL). After acidification to pH 5 and removal of solvents under reduced pressure, the residue was diluted with water. Final products were isolated by vacuum filtration, rinsed with water, and dried in vacuo.

1-(4-Trifluoromethyl-phenyl)-piperidine-4-carboxylic acid (3a). M.p. 198°C (dec). ^{1}H NMR (d_6-DMSO) δ: 1.53–1.63 (m, 2H), 1.85–1.89 (m, 2H), 2.43–2.48 (m, 1H), 2.87–2.93 (m, 2H), 3.75–3.80 (m, 2H), 7.03 (d, 2H, $J = 8.8$ Hz), 7.46 (d, 2H, $J = 9.0$ Hz), 12.23 (br s, 1H). MS (APCI+): 315 [100%, M + CH_3CN + H], 274 [50%, M + H]+. Anal. calcd. for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.35; H, 5.17; N, 5.00.

1-(3-Cyano-phenyl)-piperidine-4-carboxylic acid (3b). M.p. 150–152°C. ^{1}H NMR (d_6-DMSO) δ: 1.53–1.63 (m, 2H), 1.84–1.89 (m, 2H), 2.39–2.47 (m, 1H), 2.79–2.86 (m, 2H), 3.70–3.76 (m, 2H), 7.10 (d, 1H, $J = 7.25$ Hz),

7.24–7.26 (m, 1H), 7.30–7.37 (m, 2H), 12.23 (br s, 1H). MS (APCI+): 231 [100%, M + H]+. Anal. calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.07; H, 6.25; N, 11.8.

1-(3,5-Difluoro-phenyl)-piperidine-4-carboxylic acid (3c). M.p. 138–140°C. ^{1}H NMR (d_6-DMSO) δ: 1.53–1.60 (m, 2H), 1.82–1.86 (m, 2H), 2.40–2.48 (m, 1H), 2.80–2.87 (m, 2H), 3.66–3.71 (m, 2H), 6.38–6.44(m, 1H), 6.55–6.62 (m, 2H), 12.23 (s, 1H). MS (APCI+): 242 [100%, M + H]+. Anal. calcd. for $C_{12}H_{13}F_2NO_2$: C, 59.75; H, 5.43; N, 5.81. Found: C, 59.87; H, 5.54; N, 5.77.

1-(3,5-*bis*-Trifluoromethyl-phenyl)-piperidine-4-carboxylic acid (3d). M.p. 166–168°C. ^{1}H NMR (d_6-DMSO) δ: 1.55–1.65 (m, 2H), 1.88–1.92 (m, 2H), 2.43–2.50 (m, 1H), 2.90–2.97 (m, 2H), 3.83–3.88 (m, 2H), 7.25 (s, 1H), 7.44 (s, 2H), 12.25 (br s, 1H). MS (APCI+): 340 [100%, M − H]+. Anal. calcd. for $C_{14}H_{13}F_6NO_2$: C, 49.28; H, 3.84; N, 4.10. Found: C, 49.40; H, 3.99; N, 4.10.

1-(2-Fluoro-5-methyl-phenyl)-piperidine-4-carboxylic acid (3e). M.p. 108–110°C. ^{1}H NMR (d_6-DMSO) δ: 1.62–1.66 (m, 2H), 1.88–1.92 (m, 2H), 2.23 (s, 3H), 2.31–2.39 (m, 1H), 2.65–2.71 (m, 2H), 3.24–3.29 (m, 2H), 6.70–6.74 (m, 1H), 6.80–6.83 (m, 1H), 6.93–6.98 (m, 1H), 12.20 (s, 1H). MS (APCI+): 238 [100%, M + H]+. Anal. calcd. for $C_{13}H_{16}FNO_2$: C, 65.81; H, 6.80; N, 5.90. Found: C, 65.63; H, 6.73; N, 5.77.

1-(2-Methoxy-phenyl)-piperidine-4-carboxylic acid (3f). M.p. 129–131°C. ^{1}H NMR (d_6-DMSO) δ: 1.65–1.72 (m, 2H), 1.85–1.89 (m, 2H), 2.29–2.33 (m, 1H), 2.53–2.60 (m, 2H), 3.25–3.30 (m, 2H), 3.76 (s, 3H), 6.84–6.92 (m, 4H), 12.15 (s, 1H). MS (APCI−): 234 [100%, M − H]+. Anal. calcd. for $C_{15}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.04; H, 7.34; N, 5.81.

1-*o*-Tolyl-piperidine-4-carboxylic acid (3g). M.p. 156–158°C. ^{1}H NMR (d_6-DMSO) δ: 1.65–1.75 (m, 2H), 1.88–1.92 (m, 2H), 2.21 (s, 3H), 2.30–2.37 (m, 1H), 2.57–2.63(m, 2H), 2.98–3.02 (m, 2H), 6.90–6.98 (m, 2H), 7.09–7.14 (m, 2H), 12.19 (br s, 1H). MS (APCI+): 220 [100%, M + H]+. Anal. calcd. for $C_{15}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.58; H, 7.99; N, 6.30.

NOTE ADDED IN PROOF

Since completion of this work, a report has appeared by Wan, Y.; Alterman, M.; Hallberg, A. Palladium-catalyzed amination of aryl bromides using temperature controlled microwave heating. Synthesis, **2002**, (*11*), 1597–1600.

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